Why Use the Oral Glucose Tolerance Test?

RONALD P. STOLK, MD
TREVOR J. ORCHARD, MD
DIEDERICK E. GROBBEE, MD

The hallmark of diabetes is a chronic elevation of the blood glucose level. Thus, a single blood glucose measurement is not always sufficient to make the diagnosis. In particular, recent food intake strongly affects the levels of glucose and glucose-regulating hormones. To overcome these problems, fasting blood samples are taken to assure a glucose measurement that can be compared with previous values and with those in other patients. For a more detailed and sensitive assessment of the glucose metabolism, the oral glucose tolerance test (OGTT) was introduced, particularly for those without overt symptoms. However, in clinical practice the OGTT is often regarded as a cumbersome, time-consuming, and patient-unfriendly procedure. When diabetes is suspected in symptomatic subjects (presenting with typical diabetes symptoms, ranging from thirst and frequent urination to ketoacidotic coma) or in subjects with complications, the (random) serum glucose level is usually unequivocally raised. This suggests that for a clinician the use of the OGTT to diagnose symptomatic diabetes may be very limited in those cases. Nonetheless, in screening programs, clinical research, and population-based epidemiological studies, where participants often lack diabetes symptoms or complications, an OGTT is commonly used to detect diabetes, thus adding to the diabetic "pool" an equal-sized group of subjects with unrecognized diabetes. As a result, a potential divergence between clinical practice and epidemiological research, which should provide knowledge relevant to clinical practice, may exist.

In this commentary, we discuss the diagnosis of diabetes, impaired glucose tolerance (IGT), and insulin resistance by the OGTT in the context of clinical practice and epidemiological research.

CRITERIA FOR THE OGTT —

Over a decade ago, the National Diabetes Data Group (NDDG) of the National Institutes of Health (1) and an Expert Committee of the World Health Organization (WHO) (2) published guidelines for the OGTT based on a glucose load of 75 g, which have been internationally accepted. The criteria for the diagnosis of diabetes and IGT are given in Table 1. In addition to the WHO criteria, the NDDG requires an intermediate glucose measurement between the fasting and 2-h sample to be >11.1 mmol/l (200 mg/dl) for the diagnosis of diabetes or IGT. In epidemiological studies the intermediate blood sample may be omitted, making the two criteria identical (1). No uniform criteria exists for diagnosis of insulin resistance.

DIAGNOSING DIABETES IN CLINICAL PRACTICE —

Physicians diagnose and treat diabetes primarily to reduce the risk of diabetes complications rather than to treat the disease itself. Recently, McCance et al. (3) have reported on the association between different glycemic measures and the incidence of diabetic retinopathy and nephropathy in a group of Pima Indians without diabetes at baseline. In their study, fasting plasma glucose (FPG), 2-h post-load plasma glucose, and glycated hemoglobin were all good predictors of the incidence of diabetic complications. The onset of diabetes was equally well predicted by these three glycemic variables (3).

Clinically, it seems reasonable not to routinely use the OGTT to diagnose diabetes. Both the NDDG and the WHO guidelines indicate that in the presence of symptoms, the diagnosis can be made using a single (fasting or nonfasting) blood glucose measurement. This is also recommended in guidelines for clinical practice, such as those from the American Diabetes Association (4): diabetes is diagnosed when the plasma glucose exceeds 11.1 mmol/l (200 mg/dl) and "classic symptoms of diabetes" (polydipsia, polyuria, polyphagia, and weight loss) are present, or when the FPG twice exceeds 7.8 mmol/l (140 mg/dl). If diabetes is not confirmed by one of these tests, but still suspected, an OGTT is performed.

A survey among 174 physicians in

From the Department of Epidemiology & Biostatistics (R.P.S., D.E.G.), Erasmus University Medical School, Rotterdam, The Netherlands; and the Department of Epidemiology (T.J.O.), Graduate School of Public Health, Pittsburgh, Pennsylvania.

Address correspondence and reprint requests to Dr. Ronald P. Stolk, Department of Epidemiology & Biostatistics, Erasmus University Medical School, P.O. Box 1738, 3000 DR Rotterdam, The Netherlands.

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FPG, fasting plasma glucose; IGT, impaired glucose tolerance; NDDG, National Diabetes Data Group; NIDDM, non-insulin-dependent diabetes mellitus; OGTT, oral glucose tolerance test; WHO, World Health Organization.

Table 1—*Diagnostic criteria for the OGTT according to WHO guidelines (2)*

	Diabetes	IGT	Normoglycemia
Fasting	≥7.8 mmol/l (≥140 mg/dl)	<7.8 mmol/l (<140 mg/dl)	<7.8 mmol/l (<140 mg/dl)
2 h post-load	≥11.1 mmol/l (≥200 mg/dl)	7.8–11.1 mmol/l (140–200 mg/dl)	<7.8 mmol/l (<140 mg/dl)

Data are venous plasma glucose concentrations.

Pittsburgh showed that these guidelines correspond well with current practice (5). The physicians were randomly selected from the Internal Medicine and Family Practice listings in the telephone directory and the attending faculty in the Department of Internal Medicine. They were asked to indicate which tests they use if diabetes is suspected. Seventy-six physicians returned the questionnaire, mainly internists (84%). The median time since their graduation in medicine was 10 years. Only one of the physicians used the OGTT as a first test, and more than two-thirds (70%) never used it. FPG (64%), random blood glucose (28%), and urinalysis (13%) were most frequently used. Of the hospital-based physicians, 25% occasionally used the OGTT, mostly as a second test, whereas 42% of the nonhospital physicians used it, mainly as third test. Reported diagnostic cutoff values differed remarkably. The range for FPG was 5.6–11.1 mmol/l (100–200 mg/dl), whereas upper limits for the random blood glucose ranged between 6.1 and 16.7 mmol/l (110 and 300 mg/dl). The American Diabetes Association guidelines (7.8 and 11.1 mmol/l [140 and 200 mg/dl], respectively) were used by 50% and 33% of the physicians, more so by hospital physicians.

DIAGNOSING DIABETES IN EPIDEMIOLOGICAL RESEARCH

— The number of epidemiological studies on diabetes and its complications is constantly increasing. The OGTT is commonly used in these studies. According to the WHO guidelines, only the 2-h post-load sample is sufficient to diagnose diabetes in these studies. When a number of single glycemic measures are compared, the 2-h post-load glucose appears to provide the best indicator of the presence of diabetes (6,7).

The OGTT is a nonphysiological procedure and the interperson variability is rather high. This variability may be due to a number of factors, including diet and exercise during the days before the test, caffeine use, smoking, medications, and stress. In a population of elderly people examined annually for 5 years, the reliability coefficient of the diagnosis according to the WHO criteria was 0.62 (8). Other researchers have found that only ~50% of the OGTTs are reproducible (9), which may be partly explained by changes in ambient temperature (10). Of subjects with IGT on the first OGTT, 40–60% are diagnosed with IGT or diabetes on a second test (11–13). The biological variation (20–35% for the post-load glucose) is difficult to control but can be minimized by more careful attention to the protocol (14). Because of the OGTT's high variability and low specificity, epidemiological studies based on a single OGTT may overestimate the prevalence of diabetes by as much as 16% (15). In spite of poor precision, the post-load glucose and the post-load insulin level have been identified as important risk factors for diabetes complications and cardiovascular disease (16).

When the 2-h post-load glucose measurement of the OGTT is used, considerably more subjects are diagnosed with diabetes compared with a single FPG. In population studies, fasting blood levels of subjects with newly diagnosed diabetes show a wide distribution, ranging in one study from <5.0 mmol/l to >30.0 mmol/l (17). As a consequence, the sensitivity of the OGTT is naturally higher, given the current criteria. When the most frequent clinical approach to diabetes diagnosis (FPG) is compared with the standard epidemiological diagnosis (OGTT), it is clear that while virtually all clinical cases are diagnosed in epidemiological studies, nearly as many unrecognized cases with nondiagnostic fasting levels are identified. Consequently, epidemiological data may not always reflect the natural history to be expected in clinical practice. In contrast, clinical criteria may classify subjects as normal in spite of deviations in glucose metabolism that have prognostic relevance. Indeed, complication rates and risk factor associations may be very different.

DIAGNOSING IGT AND INSULIN RESISTANCE

— IGT is determined by the post-load glucose value of the OGTT (Table 1). The concept of IGT has been introduced to identify subjects with a moderately disturbed glucose metabolism. Although there is a considerable difference between the NDDG and WHO criteria for IGT (18), subjects with IGT are generally hyperinsulinemic and have an increased risk of developing diabetes, as reflected in the now obsolete term *prediabetes*. In follow-up studies, deterioration to diabetes has been reported from 1.5 to 4% per year (19,20). Another reason to identify IGT is an increased risk of cardiovascular diseases (21).

Intermediate glucose measurements during the OGTT may give a better

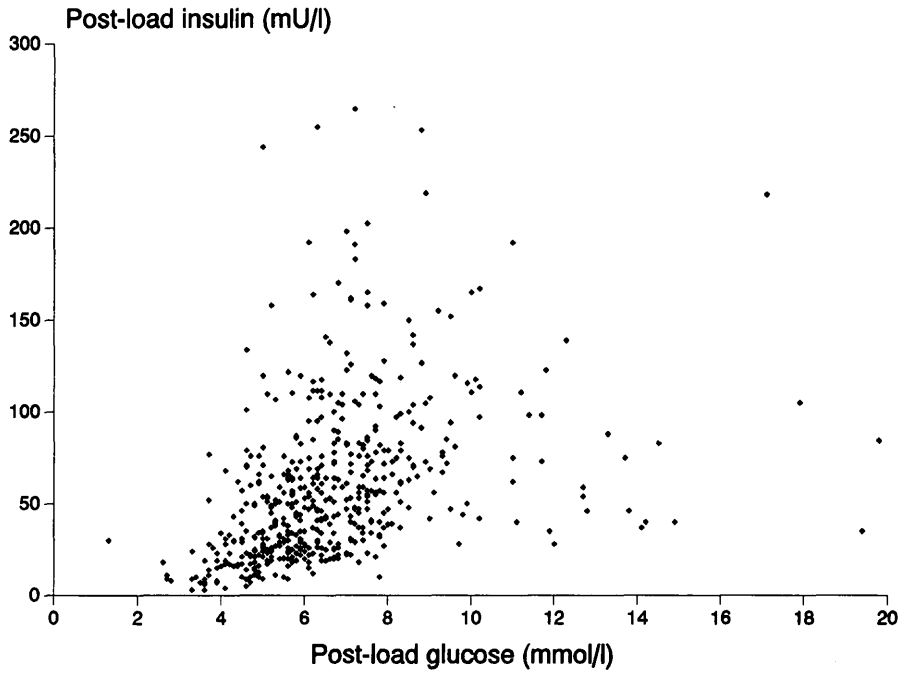

Figure 1—*Post-load glucose and insulin values of a random sample of 500 participants of the Rotterdam Study without antidiabetes medication, aged 55 to 75 years.*

estimate of the presence of IGT. This is reflected in the NDDG guidelines, which require at least one intermediate glucose level >11.1 mmol/l for the diagnosis of IGT (1). However, one disadvantage of more measurements (beyond the necessity of an extra sample) is a substantial number of nonclassified subjects, as shown in a large population study (22). This may be avoided using a single continuous measure rather than diagnostic categories. A good measure of the overall glucose response is the area under the glucose tolerance curve (23), but this method is too complex for clinical use.

Insulin resistance, probably the key factor of a cluster of cardiovascular risk factors (syndrome X or insulin resistance syndrome) (24), has been shown to precede the onset of non-insulin-dependent diabetes mellitus (NIDDM) (25,26). The gold standard for the assessment of insulin resistance is the glucose clamp technique (27). Basically, insulin resistance is a diminished ability to keep the glucose levels low with insulin levels in the normal range. In these subjects, glucose levels are slightly increased but remain below the diabetes range at the expense of raised insulin levels. This becomes more apparent if the insulin need increases, after a glucose load, for example. Therefore, insulin levels are often used as proxy for insulin resistance. It has been shown that the fasting and the post-load insulin level are good measures of insulin resistance in subjects without NIDDM (28). Recently, in nondiabetic subjects, a strong correlation was found between the mean of two fasting insulin levels and insulin sensitivity assessed by the Bergman minimal model technique ($r = 0.57$, $P < 0.025$) and with the hyperglycemic clamp ($r = 0.71$, $P < 0.005$) (M. Korytkowski, personal communication).

A further improvement may be made by using the ratio of the post-load insulin over glucose, as shown in data from the Rotterdam Study, a population-based study of chronic diseases in the elderly (29). Figure 1 gives the post-load serum insulin and glucose levels from a sample of 500 subjects without antidiabetes medication, aged 55–75 years. First, Fig. 1 demonstrates the variation in insulin response, which indicates that adjustment for the glucose level may be useful. Moreover, the insulin response is higher in the upper part of the nondiabetic glucose distribution (<11.1 mmol/l), but the variation is also greater. Some subjects in the diabetic glucose range have high insulin levels that suggest recent-onset diabetes, while others have a low insulin response that suggests a longer duration of disease.

The use of both fasting and post-load glucose levels may help to distinguish β-cell dysfunction from insulin resistance. Low insulin levels in the fasting state have only limited effect on peripheral muscle cells. An oral glucose load is largely cleared from the plasma by insulin-sensitive tissues (particularly skeletal muscle), the response of which is diminished in insulin resistance. As a consequence, subjects with only a β-cell defect may have a modestly increased post-load glucose despite fasting hyperglycemia, whereas insulin-resistant subjects show markedly increased post-load glucose levels (30). In established NIDDM, both glucose levels are often increased, reflecting both defects being present (31).

The requirement of the fasting state may sometimes cause logistic problems for the use of the OGTT in large (screening) studies, which are now restricted to the early morning. Some evidence suggests that the glucose and insulin levels after a glucose load given in a nonfasting state are as good as those in a fasting state (32). Because the post-load glucose value is the most valuable to diagnose diabetes (see above), this would permit the use of a nonfasting test in certain circumstances.

To investigate the influence of fasting, the Rotterdam Study investigators performed an OGTT twice in 69 subjects without diabetes, once nonfasting and once fasting. The glucose levels and, in particular, the insulin levels 2 h after the oral glucose load were quite comparable

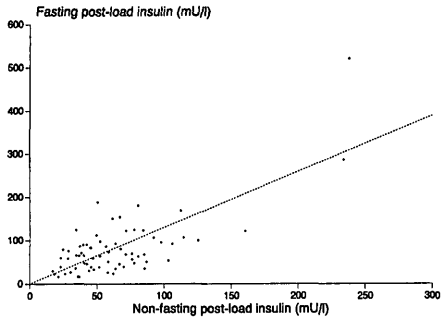

Figure 2—*Serum insulin 2 h after the nonfasting and fasting OGTT. The dotted line is the regression line* ($y = -0.15 + 1.30 \times x$).

after the fasting and the nonfasting OGTT (correlation coefficient 0.61 and 0.74 respectively, $P < 0.001$). Figure 2 shows that the post-load serum insulin is hardly influenced by the fasting state. At least these results suggest that it is not necessary to give the glucose load in the fasting state to estimate insulin resistance, raising the possibility that the OGTT, though not ideal for the clinical diagnosis of diabetes, may have a role as a poor man's (clinical) marker of insulin resistance.

CONCLUSIONS— While in clinical practice glucose intolerance is classified as diabetes or not, it is important to realize that both hyperglycemia and hyperinsulinemia represent a continuum. Any cutoff value remains arbitrary. Furthermore, within the diabetic range, increased serum glucose levels are associated with increased severity of diabetes complications, both microvascular, like retinopathy (33), and macrovascular (34). Results from trials show that increased metabolic control decreases the incidence and progression of retinopathy (35,36). In nondiabetic populations, the risk of diabetes complications, both microvascular and macrovascular, increases gradually with an increase in serum glucose (37), HbA_{1c} (38), and insulin (39).

In conclusion, it would seem desirable that clinical and epidemiological definitions (and diagnostic methodology) are comparable and that the role of the OGTT in the clinical diagnosis of diabetes is minimal. As McCance et al. (3) demonstrate in terms of prediction of diabetes complications, the OGTT can easily be replaced by FPG or HbA_{1c}, both of which, it seems, are preferentially used by clinicians anyway.

The other argument for the diagnostic use of the OGTT, i.e., to detect the "unknown" diabetic subjects, rests upon the assumption that subclinical deviations in glucose metabolism have prognostic importance. Knowledge as to whether and how to treat discovered asymptomatic diabetic subjects is clearly needed (40). If the Pima data (3) are confirmed in other studies, it would seem that the high-risk unknown diabetic subjects can be identified by simpler tests.

On the other hand, the OGTT may have a role in the evaluation of IGT/insulin resistance. In this regard, it may be used to identify subjects with an increased risk of diabetes and cardiovascular disease more precisely than with a random measurement of the serum glucose or insulin. Currently, however, there is no definitive treatment for IGT or insulin resistance. Further research, using the OGTT, may help elucidate the role of IGT and insulin resistance and indicate ways for early treatment to prevent or postpone subsequent morbidity and complications (40). The new National Institutes of Health–sponsored trial, currently named DPT2, may help resolve this issue. Eventually, the place of IGT and insulin resistance in the risk profile of cardiovascular (and diabetic) diseases should be more clearly defined so that preventive approaches, similar to those currently in operation for hypertension and hypercholesterolemia, can be developed.

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